



Design and Development of Chiral Bis-Phosphoric Acids and Enantioselective Allylic Substitution Reaction

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論文内容要旨

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論文目次

第 1 章 Introduction

第 2 章 Development of Enantioselective Allylic Substitution Reaction

第 3 章 Design and Development of Chiral Bis-Phosphoric Acids

第 4 章 Conclusion

論文内容要旨

Chapter 1. Introduction

Enantioselective reactions using organocatalyst has been actively investigated during the past decades. Among various kinds of organocatalysts, BINOL-derived phosphoric acids and derivatives have been widely utilized as the most representative chiral Brønsted acid catalyst. Although a number of enantioselective reactions have been successfully established by using these catalysts, there still remain many unresolved challenges in the chiral Brønsted acid catalysis. In order to further expand the scope of enantioselective transformations using chiral Brønsted acid, the development of new catalytic reaction systems and novel catalysts is highly desirable.

In this work, we envisioned (1) a new strategy to achieve enantioselective allylic substitution reaction which is still a formidable challenge and (2) the development of novel chiral bis-phosphoric acids derived from BINOL dimer.

Chapter 2. Development of Enantioselective Allylic Substitution Reaction

Nucleophilic allylic substitution reaction is one of the most versatile reactions in organic synthesis. Particularly, asymmetric allylic alkylation reaction is an efficient method for the synthesis of optically active allylic compounds. Whereas the field has been dominated by transition metal catalysis involving chiral π -allyl-metal intermediate, organocatalytic asymmetric transformations utilizing S_N2' process have still rarely been explored. Especially, the intermolecular version represents a formidable challenge. In this context, we envisioned that chiral Brønsted acid catalyst could accelerate the intermolecular asymmetric allylic substitution reaction through activation of a leaving group, affording chiral allyl compound. The major difficulty in the development of the intermolecular allylic substitution is not only the control of the enantioselectivity but also prevents the S_N2 reaction providing the achiral linear compound. The reaction of allyl ether having 3-nitro-2-pyridyl moiety as a leaving group with *N*-methyl indole was investigated in the presence of chiral Brønsted acid catalyst. As a result, we found that corresponding 3-allylated indoles were obtained in an enantio-enriched form.

Chapter 3. Design and Development of Chiral Bis-Phosphoric Acid

The development of strong chiral Brønsted acids is crucial to broaden the scope of enantioselective transformations due to the fact that strong acid catalysts would expand the scope of electrophilic species employed. Previously our laboratory developed chiral bis-phosphoric acids (BISPA) having a single BINOL backbone to enhance the acidity by virtue of the intramolecular hydrogen bonding interaction between the two phosphoric acid units. In our continuous effort to develop chiral Brønsted acid catalysts having high acidity, we developed structurally altered bis-phosphoric acids, which are derived from a BINOL dimer as a chiral backbone. The catalytic performance of developed catalyst was confirmed in the Diels-Alder reaction of acrolein with 1,3-dien-1-ylcarbamate. A detailed structural analysis of the newly developed BISPA was also conducted to evaluate the importance of the dihedral angle around the axial chirality in determining the stereochemical outcome of the product.

Chapter 4. Conclusion

In this doctor's thesis entitled "Design and Development of Chiral Bis-Phosphoric Acids and Enantioselective Allylic Substitution Reaction", we aimed at the development of a new strategy for a metal-free enantioselective allylic substitution reaction was envisioned based on the simultaneous activation of leaving group and nucleophile by chiral Brønsted acid catalyst using the intermolecular S_N2' reaction. The desired alkylated indole was obtained with the induction of enantioselectivity and moderate regioselectivity. In another work, a highly acidic structurally altered Bis-Phosphoric Acid catalyst derived from the BINOL dimer was developed based on rigid axial chirality and its catalytic efficiency was confirmed in enantioselective Diels-Alder reaction. A detailed structural analysis was done to evaluate the important factors inflectional on the stereochemical outcome of the product. Due to bulkiness and high acidity, we aimed that further application of this newly developed catalyst will be of great interest and it will broaden the scope of enantioselective transformations.

論文審査の結果の要旨

「Design and Development of Chiral Bis-Phosphoric Acids and Enantioselective Allylic Substitution Reaction (キラルビスリン酸の設計開発とエナンチオ選択的アリル位置換反応)」と題する Gupta Yogesh 氏提出の博士論文では、キラルブレンステッド酸触媒による触媒的不斉反応の適用範囲拡充を目的とし、「新たなキラルブレンステッド酸触媒の設計・開発」ならびに、これまでに有機分子触媒を用いた不斉反応系として報告例が限られていた「分子間不斉アリル位置換反応」に着目し、開拓を行っている。

第 2 章では、キラルブレンステッド酸触媒を用いたアリルアルコール誘導体と *N*-メチルインドールとのエナンチオ選択的アリル位置換反応の開発を行っている。これまでに遷移金属触媒を用いた不斉アリル位置換反応は数多く達成されてきたが、メタルフリー条件下での反応は、非常に限られていた。これに対し、筆者は、キラルブレンステッド酸触媒による脱離基の活性化を利用することで、効率的に分子間アリル位置換反応が進行することを見出し、目的とするアリル化されたインドール誘導体を不斉の発現と共に、得ることに成功した。

第 3 章では、光学活性 BINOL を直接連結させた「BINOL ダイマー」から誘導したビスリン酸触媒を新たに設計・合成し、アクロレインとアミドジエンとの不斉ディールズ・アルダー反応において機能評価を行っている。本触媒設計では、触媒骨格への置換基導入を短段階で行うことが可能となるとともに、その嵩高さのためにこれまで導入することが困難であった、トリフェニルシリル基を有するビスリン酸触媒の合成が可能となった。筆者は、本触媒が不斉ディールズ・アルダー反応において有効に機能し、高いエナンチオ選択性を示すことを明らかにした。また、以前に当研究室で開発されたビスリン酸触媒との比較実験並びに、計算化学的手法に基づいた触媒構造の解析を行っている。その結果、触媒骨格が構築する二面角の違いが効果的な不斉反応場の構築において重要であることを明らかにした。この構造的特徴に関する知見は、新たな触媒の設計開発にも繋がる、大変意義深い成果である。

これらの研究成果は、著者が自立して研究活動を行う上で必要な高度の研究能力と学識を有することを示している。したがって、Gupta Yogesh 提出の博士論文は、博士（理学）の学位論文として合格と認める。